

Adherence to Antiretroviral Therapy in Children and Adolescents with HIV

Updated: Apr. 11, 2022

Reviewed: Apr. 11, 2022

Panel's Recommendations
<ul style="list-style-type: none">• Strategies to maximize adherence should be discussed before and/or at initiation of antiretroviral therapy (ART) and before changing regimens (AIII).• Adherence to therapy must be assessed and promoted at each visit, and strategies to maintain and/or improve adherence must be continually explored (AIII).• In addition to viral load monitoring, at least one other method of measuring adherence to ART should be used (AIII).• Once-daily antiretroviral regimens and regimens with a low pill burden should be prescribed whenever feasible (AII*).
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</p> <p>Rating of Evidence: I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term clinical outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion</p> <p>†Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents</p>

Background

Adherence to antiretroviral therapy (ART) is a principal determinant of virologic suppression. Suboptimal adherence may include missed or late doses, treatment interruptions and discontinuations, and subtherapeutic or partial dosing.^{1,2} Poor adherence will result in subtherapeutic plasma antiretroviral (ARV) drug concentrations, facilitating the development of resistance to one or more drugs in a given ARV regimen and possible cross-resistance to other drugs in the same class. Multiple factors—including regimen potency, pharmacokinetics, drug interactions, viral fitness, and the genetic barrier to ARV resistance—influence the adherence–resistance relationship.³⁻⁵ In addition to compromising the efficacy of the current regimen, suboptimal adherence can limit the options for future effective ARV drug regimens in patients who develop multidrug-resistant HIV; it also can increase the risk of secondary transmission of drug-resistant virus.

Poor adherence to ARV drugs is commonly encountered in the treatment of children and adolescents with HIV. A variety of factors—including medication formulation, frequency of dosing, drug toxicities and side effects, and the child's age and developmental stage, as well as psychosocial, behavioral, and sociodemographic characteristics of children and caregivers—have been associated with inadequate adherence. However, no consistent predictors of either good or poor adherence in children have been identified.⁶⁻⁸ Several studies have demonstrated that adherence is not static and can vary with time on treatment.⁹ More recently, findings from the U.S. Pediatric HIV/AIDS Cohort Study (PHACS) demonstrated that the prevalence of nonadherence increased with age. Among 381 children and adolescents with perinatally acquired HIV, the prevalence of nonadherence increased from 31% to 50% ($P < 0.001$), and the prevalence of unsuppressed viral loads increased from 16% to 40% ($P < 0.001$) between pre-adolescence and late adolescence/young adulthood.¹⁰ Similarly, in a

report from the Early Pediatric Initiation Canada Cure Cohort, only 73% of the children initiated on ART maintained viral suppression 3 years after it was first achieved.¹¹ These findings illustrate the difficulty of maintaining high levels of adherence and underscore the need to work with patients and their families to ensure that adherence education, support, and assessment are integral components of care.

Specific Adherence Issues in Children

Adherence is a complex health behavior that is influenced by drug regimen, patient and family factors, and the patient–provider relationship.^{12,13} Despite improvements over the last several years, the availability of once-daily and single-tablet ARV regimens and palatable formulations for infants and young children are limited.¹⁴ Furthermore, infants and children are dependent on others for medication administration; adult caregivers may face barriers that undermine adherence in children, including forgetting doses, changes in routine, being too busy, and child refusal.^{15,16} Caregivers also may be inadequately prepared to support their child’s adherence. In a study of communication strategies among caretakers of children with perinatally acquired HIV in rural South Africa, many caregivers used coercion and threats of grave consequences of nonadherence as a communication strategy to enforce adherence.¹⁷ Furthermore, some caregivers may place too much responsibility for managing medications on older children and adolescents before they are developmentally able to undertake such tasks.¹⁸ Adherence also may be jeopardized by social and health issues within a family (e.g., substance use, poor physical or mental health, unstable housing, poverty, violence, involvement with the criminal justice system, limited social support).¹⁹⁻²²

Adherence Assessment and Monitoring

Clinicians should begin assessing potential barriers to adherence and discussing the importance of adherence with patients before initiating or changing an ARV regimen. Evaluations should assess social and behavioral factors that may influence adherence and should identify individual needs for intervention. Clinicians should ask patients about their experience with taking medications, as well as concerns and expectations about treatment. Before beginning treatment, it is important that the patient explicitly agree to the treatment plan, which should include strategies to support adherence. It is also important to alert patients to potential adverse effects (AEs) of ARV drugs (e.g., nausea, headaches, abdominal discomfort, sleep disturbances), explain how they can be managed, and emphasize the importance of informing the clinical team if they occur.

A routine adherence assessment should be incorporated into every clinical visit. Adherence is difficult to assess accurately; different methods of assessment have yielded different results, and each approach has limitations.²³⁻²⁵ Viral load monitoring is the most useful indicator of adherence and is a routine component of monitoring individuals who are on ART (see [Plasma HIV-1 RNA \[Viral Load\] and CD4 Count Monitoring](#) in the [Adult and Adolescent Antiretroviral Guidelines](#)). It also can be used as positive reinforcement to encourage continued adherence.²⁶ In addition to viral load monitoring, clinicians should use at least one other method to assess adherence.²⁴ Table 13 below includes common approaches to monitoring medication adherence.

Strategies to Improve and Support Adherence

When concerns about adherence emerge, a patient should be seen and/or contacted frequently (by telephone, text message, email, and social networking as allowed within the context of local legal and regulatory requirements) to assess adherence and to determine the need for strategies that can improve and support adherence. During the first month of treatment (or a regimen change), a patient can be contacted weekly, or even daily, if necessary. The growing use of telemedicine visits, which

allow remote and often face-to-face contact, provides new opportunities to support families and visualize ART handling/swallowing, as well as to conduct directly observed therapy (DOT) in the home setting (see [Clinical and Laboratory Monitoring of Pediatric HIV Infection](#) and [Table 3](#)).

Strategies should include simplifying the ARV drug regimen, developing treatment plans that integrate medication administration into daily routines (e.g., associating medication administration with daily activities, such as brushing teeth), and optimizing the use of social and community support services. Multifaceted approaches that include regimen-related strategies; educational, behavioral, and supportive strategies focused on children and families; and strategies that focus on health care providers may be more effective than one specific intervention. Table 14 below summarizes some of the strategies that can be used to support and improve adherence to ARV medications. The Centers for Disease Control and Prevention (CDC) offers a [web-based toolkit](#) (consisting of four evidence-based HIV medication adherence strategies) to HIV care providers.²⁷ A recent analysis using the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)–Adolescent model of HIV disease and treatment modeled the impact of a 12-month hypothetical adherence intervention (based on an interactive smartphone-based reminder system) among youth with HIV in the United States. Compared with the standard of care, the analysis showed that youth-targeted adherence interventions, even with modest efficacy to improve virologic suppression, could improve life expectancy, prevent onward HIV transmissions, and be cost-effective.²⁸

Regimen-Related Strategies

To the extent possible, ARV regimens should be simplified with respect to the number of pills or volume of liquid prescribed as well as the number of daily doses, and drugs in the regimen should be chosen to minimize drug interactions and AEs.²⁹ Efforts should be made to reduce the pill burden and pill size and to prescribe once-daily ARV regimens and single-tablet regimens whenever feasible (see Table 16 in [Management of Children Receiving Antiretroviral Therapy](#)). With the introduction of new ARV drug classes and a wider array of once-daily formulations—including some medications that are now available in a small pill size—more options for less toxic, simplified regimens are now available, particularly for older children and adolescents. Several studies in adults have demonstrated better adherence with once-daily ARV regimens than with twice-daily regimens, and better adherence with single-tablet formulations than with multiple-tablet regimens.^{14,30-33} [Appendix A, Table 1](#) shows which ARV drugs are available in fixed-dose combination (FDC) tablets, and [Appendix A, Table 2](#) provides information about minimum body weight requirements and other considerations when using FDC tablets in children.

When nonadherence is related to the poor palatability of a liquid formulation or crushed pills, the offending taste can sometimes be masked with a small amount of flavoring syrup or food if simultaneous administration of food is not contraindicated (see [Appendix A: Pediatric Antiretroviral Drug Information](#)).³⁴ Unfortunately, the taste of lopinavir/ritonavir cannot be masked with flavoring syrup. A small study of children and youth aged 4 years to 21 years found that training children to swallow pills was associated with improved adherence at 6 months post-training.³⁵ Finally, if drug-specific toxicities are thought to be contributing to nonadherence, efforts should be made to alleviate the AEs by changing the particular drug (or, if necessary, the drug regimen) when feasible.

Patient/Family-Related Strategies

Patient and caregiver education is an essential component of establishing good medication adherence in children. Educating families about adherence should begin before initiating or changing ARV medications and should include a discussion of the goals of therapy, the importance of optimizing adherence, and the specific plans for supporting and maintaining a child's medication adherence.

Caregiver adherence education strategies should include the provision of both information and adherence tools, such as written and visual materials; a daily schedule illustrating times and doses of medications; and demonstration of the use of syringes, medication cups, and pill boxes. Additionally, it may be helpful to assess the medication adherence of the caregiver or other household members who currently take ARV drugs or other chronic medications.

Several behavioral tools can be used to integrate taking medications into a child's daily routine. The use of behavior modification techniques, especially the application of positive reinforcements and the use of small incentives (including financial incentives) for taking medications, can be effective tools to promote adherence.³⁶ Treating mental health disorders (e.g., depression) may facilitate adherence to complex ARV regimens.^{37,38}

If the child has not been informed of their HIV status, HIV disclosure should be discussed with the caregivers. In a recent review that explored the relationship between ART adherence and disclosure, five studies linked disclosure to improved adherence, four studies found that disclosure led to worse adherence among study participants, and five studies found no association.³⁹ In interviews with caregivers of children with HIV in South Africa, investigators found that caregivers who had disclosed to their child that they (i.e., the child) were living with HIV were truthful in their communications and named the disease as HIV, but communication about HIV was infrequent and focused on pill taking. By comparison, those who had not disclosed used deception, deflection, and coercion in response to health-related questions and to enforce adherence.¹⁷ The decision to disclose HIV status should not necessarily be expected to improve adherence but should be based on a comprehensive assessment of the psychosocial milieu and the needs of the child and family.

In poorly adherent children who are at risk of disease progression and who have severe and persistent aversion to taking medications, the use of a gastrostomy tube may be considered.⁴⁰ If adequate resources are available, home-nursing interventions or DOT also may be beneficial. The evidence is mixed as to the efficacy of programs that are designed to improve adherence through DOT, but DOT may still be a useful strategy for some patients.⁴¹⁻⁴³ Among 50 adolescents on atazanavir-based second-line therapy participating in a study of modified directly administered ART (mDAART), there was a significant increase in self-reported adherence (relative risk [RR] = 0.1; 95% confidence interval [CI], 0.02–0.8; $P = 0.023$) but a nonsignificant increase in virological suppression to <1,000 copies/mL ($P = 0.105$) among those randomized to the intervention arm compared to the standard of care arm.⁴⁴ A recent randomized controlled trial (RCT) of a 12-week multicomponent intervention—including remote coaching, electronic dose monitoring, and tailored outreach (Triggered Escalating Real-Time Adherence)—for viremic youth in the United States demonstrated improved adherence but not viral suppression compared with the standard of care.²¹

Other strategies to support adherence include using mobile applications (apps) that remind patients to take medications; setting patients' cellphone alarms to go off at medication times; sending text-message reminders; conducting motivational interviews; providing pill boxes, blister packaging, and other adherence support tools; and delivering medications to the home. The CDC has an adherence toolbox, which includes a free mobile app (Every Dose Every Day mobile app) that is available through its [website](#).

Several systematic reviews evaluating the use of mobile phone technologies to improve ART adherence (mHealth) have been published. In a recent review, the authors found what they described as “ambiguous results with high variability” about the effectiveness of mHealth interventions to improve adherence in low- and middle-income countries.⁴⁵ Of 17 studies, 56% reported a statistically significant positive impact of mHealth on adherence; 44% reported insignificant results. Another systematic review reported that the efficacy of mobile short message service (SMS) interventions

varied depending on the specific SMS intervention tested.⁴⁶ A third systematic review of the effectiveness of using mobile phone interventions to improve adherence to ART also reported mixed results; effectiveness varied depending on the measured outcomes and the specific intervention (e.g., whether the study evaluated the use of texts or the use of phone calls).⁴⁷ It should be noted, however, that the evidence base for effective adherence interventions in adolescents and young adults who are taking daily ART is limited.⁴⁸⁻⁵⁴

Lowenthal et al. examined the association between medication-specific reactance—an aversive response to perceived threats against personal agency (behavioral freedom)—and treatment failure in a cohort of adolescents with HIV in Botswana. The authors explain that reactant individuals may hear health messaging as a threat to their perceived freedom and respond by engaging in the opposed behavior. In the study, adolescents were asked to rate the following two questions on a 5-point scale, ranging from definitively false (1) to definitively true (5): (1) whether verbal reminders to take medicines made them want to avoid taking them, and (2) whether they felt anger when reminded to take medicines. Reactant adolescents, those scoring >4, had a 2.05-fold (95% CI, 1.23–3.41) greater odds of treatment failure than non-reactant youth ($P = 0.043$). Psychological reactance needs further study and may provide some insight into adherence behaviors among youth; it also may be important to consider in adherence counseling and in designing interventions.⁵⁵

Two recently published studies provided evidence of the efficacy of peer-based interventions to improve ART adherence and viral suppression among adolescents and young people living with HIV in Africa. In Project YES! in Ndola, Zambia, 273 youth aged 15 to 24 years receiving HIV care in four health facilities—including a children’s hospital—were randomly assigned to monthly meetings with youth peer mentors. At 6 months, viral suppression improved in both study arms, but among participants in care at the pediatric clinic, the rate of viral suppression increased from 37.5% to 70.5% in the intervention arm versus the comparison arm, 60.3% to 59.4% (interaction term odds ratio [OR], 4.66; 95% CI, 1.84–11.78).⁵⁶ Mavhu et al. tested the efficacy of a peer-led differentiated service delivery intervention on HIV clinical outcomes among adolescents with HIV aged 13 to 19 years in rural Zimbabwe. Sixteen clinics were randomized to standard of care or the enhanced intervention in which adolescents were assigned a community adolescent treatment supporter; attended monthly support group; and received text messages, calls, home visits, and clinic-based counseling. Overall, 212 adolescents were recruited at intervention sites and 284 at control sites, with a median age of 15 years. At 96 weeks, among 479 adolescents with data, 52 (25%) adolescents in the intervention arm versus 97 (36%) in the control arm had viral load >1,000 copies/mL or had died (adjusted prevalence ratio 0.58; 95% CI, 0.36–0.94; $P = 0.03$). The study reported 28 deaths (17 in the intervention arm, 11 in the control arm) and 57 hospital admissions (20 in the intervention arm, 37 in the control arm). These studies demonstrate that peer-based interventions have the potential to improve adherence and health outcomes among youth with HIV.⁵⁷

Further evidence of the efficacy of peer-support interventions for people living with HIV comes from a recent systematic review and meta-analysis, including 20 RCTs comprising 7,605 participants from nine countries. The authors found superior retention in care (RR 1.07; 95% CI, 1.02–1.12 at 12 months follow-up) and better ART adherence (RR 1.06; 95% CI, 1.01–1.10 at 3 months follow-up) but no statistically significant difference in viral suppression (RR = 1.02; 95% CI, 0.94–1.11 at 6 months follow-up) among peer-support participants.⁵⁸

Health Care Provider–Related Strategies

To improve and support ART adherence, providers should maintain a nonjudgmental attitude, establish trust with patients and caregivers, and identify mutually acceptable goals for care. Providers can improve adherence through their relationships with patients’ families. This process begins early

in a provider's relationship with a family, when the clinician obtains explicit agreement about the medication and treatment plan and any further strategies to support adherence. Fostering a trusting relationship and engaging in open communication are particularly important. Focus groups and semi-structured interviews were conducted with adolescents and their caregivers participating in a longitudinal adherence study. Participants who self-reported high adherence but for whom electronically monitored data reflected low adherence were selected. Adolescents described hiding and discarding pills and lying about their adherence. Adolescents and parents considered negative feedback for prior poor adherence as motivation for efforts to hide current poor adherence. The authors suggest that positive feedback for truth-telling may help develop family and staff alliances in support of adherence.⁵⁹

Provider characteristics that have been associated with improved patient adherence in adults include consistency, willingness to give information and ask questions, technical expertise, and commitment to follow-up. Creating an environment in the health care setting that is child-centered and includes caregivers in adherence support also has been shown to improve treatment outcomes. Immigrant children and families may face unique social and cultural issues; it is important to recognize these issues and facilitate linkage to community resources, particularly for families who are recent immigrants. Providing comprehensive multidisciplinary care (e.g., with nurses, case managers, pharmacists, social workers, psychiatric care providers) also may better serve more complex patient and family needs, including adherence. Provider-initiated education about viral load and counseling targeted at understanding viral load results, the health benefits of undetectable viral load, and the undetectable = untransmittable (U = U) concept are other strategies providers can use.

Table 13. Approaches for Monitoring Medication Adherence

Routine Assessment of Medication Adherence in Clinical Care ^a	Description
Monitor viral load.	Viral load monitoring should be done more frequently after initiating or changing medications. ^a
Assess a quantitative self-report of missed doses.	Ask the patient and/or caregiver about the number of missed doses over a defined period (1, 3, or 7 days).
Request a description of the medication regimen.	Ask the patient and/or caregiver about the name, appearance, and number of medications and how often the medications are taken.
Assess barriers to medication administration.	Engage the patient and caregiver in a dialogue about potential barriers to adherence and strategies to overcome them.
Monitor pharmacy refills.	Approaches include a pharmacy-based or clinic-based assessment of on-time medication refills.
Employ telemedicine to monitor and support medication administration.	Telemedicine visits allow remote and often face-to-face contact and provide new opportunities to support families; to visualize ART preparation, handling, and swallowing; and to conduct DOT in the home setting.
Conduct announced and unannounced pill counts.	Approaches include asking patients to bring medications to the clinic, conducting home visits, or providing referral to community health nursing.
Targeted Approaches to Monitoring Adherence in Special Circumstances	Description
Implement DOT in person and via telemedicine.	Include a brief period of hospitalization if indicated.
Measure drug concentration in plasma or DBS.	Measuring drug concentrations can be considered for particular drugs.
Approaches to Monitoring Medication Adherence in Research Settings	Description
Measure drug concentrations in hair.	Measuring hair drug concentrations can be considered for particular drugs; it provides a good measure of adherence over time. ^{23,60,61}
Use electronic monitoring devices.	Approaches include MEMS caps and Wisepill.
Use mobile phone-based technologies.	Approaches include interactive voice response, text messaging, and mobile apps.

^a See [Clinical and Laboratory Monitoring of Pediatric HIV Infection](#) regarding the frequency of adherence assessment after initiating or changing therapy.

Key: apps = applications; ART = antiretroviral therapy; DBS = dried blood spots; DOT = directly observed therapy; MEMS = Medication Event Monitoring System

Table 14. Strategies to Improve Adherence to Antiretroviral Medications

Initial Intervention Strategies
<ul style="list-style-type: none">• Establish trust and identify mutually acceptable goals for care.• Obtain explicit agreement on the need for treatment and adherence.• Identify depression, low self-esteem, substance abuse, or other mental health issues in the child/adolescent and/or the caregiver that may affect adherence. Evaluate and initiate treatment for mental health issues before starting ARV drugs, if possible.• Determine whether the child is aware of their HIV status. Consider talking to the child's caregivers about disclosing this information to the child in a developmentally appropriate way.• Identify family, friends, health team members, and others who can support adherence.• Educate the patient and family about the critical role of adherence in therapy outcome, including the relationship between partial adherence and resistance and the potential impact on future drug regimen choices. Develop a treatment plan that the patient and family understand and to which they feel committed.• Work with the patient and family to make specific plans for taking medications as prescribed and for supporting adherence. Assist them in arranging administration during day care, school, and in other settings, when needed. Consider home delivery of medications.• Establish a patient's readiness to take medication by staging practice sessions or by other means.• Schedule a home visit or telemedicine visit to review medications and determine how they will be administered in the home setting.• In certain circumstances, consider a brief period of hospitalization at the start of therapy for patient education and to assess the tolerability of the chosen medications.
Medication Strategies
<ul style="list-style-type: none">• Choose the simplest regimen possible; reduce dosing frequency, pill size, and number of pills (see Appendix A, Table 1 and Appendix A, Table 2).• When choosing a regimen, consider the patient's daily and weekly routines and potential variations in patient and family activities.• Choose the most palatable medicine possible (pharmacists may be able to add syrups or flavoring agents to increase palatability).• Choose drugs with the fewest AEs; provide anticipatory guidance for managing AEs.• Simplify food requirements for medication administration.• Prescribe drugs carefully to avoid adverse drug–drug interactions.• Assess pill-swallowing capacity and offer pill-swallowing training and aids (e.g., pill-swallowing cup, pill glide). Adjust pill size as needed.
Follow-Up Intervention Strategies
<ul style="list-style-type: none">• Have more than one member of the multidisciplinary team monitor adherence at each visit and in between visits by telephone, email, text, and social media, as needed.• Provide ongoing support, encouragement, and understanding of the difficulties associated with maintaining adherence to daily medication regimens.• Provide education and counseling that explain the meaning and significance of viral load results.• Use patient education aids, including pictures, calendars, and stickers.• Encourage the use of pill boxes, reminders, mobile apps, alarms, and timers.• Provide follow-up clinic visits, telephone calls, text messages, and telemedicine visits to support and assess adherence.

- Provide access to support groups, peer groups, or one-on-one counseling for caregivers and patients, especially for those with known depression or drug use issues that decrease adherence.
- Provide pharmacist-based adherence support, such as medication education and counseling, blister packs, refill reminders, automatic refills, and home delivery of medications.
- Consider DOT at home, in the clinic, or, in certain circumstances, during a brief period of inpatient hospitalization.
- Consider gastrostomy tube use in certain circumstances.
- Information on other interventions to consider can be found at the [Complete Listing of Medication Adherence Evidence-Based Behavioral Interventions](#) on the CDC's website.
- Consult the CDC [Every Dose Every Day toolkit](#).

Key: apps = applications; AE = adverse effect; ARV = antiretroviral; CDC = Centers for Disease Control and Prevention; DOT = directly observed therapy

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